REMARKS

Summary of the Office Action

Prior to the entry of the present amendment, claims 1-21 are pending in the application. Claims 5-21, due to restriction requirement, are withdrawn from consideration. Claims 1-4 are rejected under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 112, second paragraph. Claims 1, 2, and 4 are rejected under 35 U.S.C. § 103 as unpatentable over Duyk et al. (U.S. Patent No. 6,531,644; hereafter "Duyk et al.") in view of Unhavaithaya et al. (Cell 111:991-1002, 2002; hereafter "Unhavaithaya et al.").

Priority

Applicants have re-written claim 1 as 4 independent claims: amended claim 1 is directed to a loss of function mutation in *lin(n3628* (SEQ ID NO: 24); new claim 23 directed to a loss of function mutation in *lin(4256)* (SEQ ID NO: 26); new claim 27 is directed to a loss of function mutation in *lin-65* (SEQ ID NO: 28); and new claim 31 is directed to a loss of function mutation in *mep-1*(SEQ ID NO: 2).

Applicants submit that amended claim 1, and its dependent claims, and new claim 31, and its dependent claims, are entitled, under 35 U.S.C. § 119(e), to benefit of the filing dates of Provisional Application Serial No. 60/437,821 filed January 20, 2003, and Provisional Application Serial No. 60/410,160 filed September 12, 2002. The disclosure of Provisional Application Serial Nos. 60/437,821 and 60/410,160 provides support for amended claim 1, and its dependent claims, and new claim 31, and its dependent claims, that meets the requirements of 35 U.S.C. § 112, first paragraph (see, page 61, line 1, to page 62, line 24; page 63, line 10, to page 64, line 20; and page 190, lines 1-5 of Provisional Application Serial No. 60/437,821; and page 61, line 1, to page 62, line 24; page 63, line 10, to page 64, line 20; and page 190, lines 1-5 of Provisional Application Serial No. 60/410,160).

Summary of the Invention

Applicants have discovered new members of the synMuv gene family. Applicants provide methods for the identification of candidate compounds that may be used to treat a neoplasia in patients. The methods require measurement of cell proliferation in a cell having a loss of function mutation in a Class B synMuv gene: *mep-1*, *lin(n3628)*, *lin(n4256)*, or *lin-65*; and a second loss of function mutation in a Class A synthetic multivulval gene following exposure of the cell to a candidate compound.

Amendments to the Claims

As described above, the subject matter of claim 1 has been separated into four independent claims. Claim 1 has been amended to require a loss of function mutation in a Class B synMuv gene having at least 95% sequence identity to SEQ ID NO: 24; require a second loss of function mutation in a Class A synthetic multivulval gene; specify the phenotype to be cell proliferation; and add a correlation step. Claim 4 has been canceled in view of the present amendment of claim 1. Withdrawn claims 5-21 have been canceled. New claims 22-34 have been added. Support for the amendment and new claims is found in the specification as filed, for example, at page 1, line 29, to page 2, line 7; page 3, lines 1-25; page 3, lines 26-29; pages 29-30, Table 1; and page 54, Table 5.

No new matter has been added by the present amendment. Applicants reserve the right to pursue any canceled subject matter in this or in a continuing application.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-4 are rejected under 35 U.S.C. § 112, second paragraph for omitting an essential step. In particular, the Office states (page 4):

> The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how

> the results of the assay allow for determination. In claim 1, the correlation step is missing.

Claim 1 as amended includes a correlation step. This basis for rejection may be withdrawn.

Claims 1-4 are further rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Office states (page 4):

> The specification defines the genes for *lin(n3628)*, *lin(n4256)*, *lin-65*, and *mep-1*, as nucleic acids "substantially identical" to SEQ ID No's: 24, 27, 28 and M04B2.1, respectively.... A skilled artisan would not be able to ascertain the meaning of the term "substantially identical" in the context of the genes named in claim 1. It is not clear what nucleic acid sequence homology with the sequences having SEQ ID No's: 24, 27, 28 and M04B2.1 would be required to meet the limitation "substantially identical."

Claim 1 has been amended to recite a nucleic acid having at least 95% sequence identity to SEQ ID NO: 24. New claims 23, 27, and 31 recite a nucleic acid having at least 95% sequence identity to SEQ ID NO: 26, 28, and 2, respectively. This basis for the 35 U.S.C. § 112, second paragraph rejection should also be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-4 are rejected under 35 U.S.C. § 112, first paragraph for an asserted lack of written description and enablement.

Written Description

As the basis for the written description rejection, the Office states (pages 6 and 7):

> The specification (p.47) describes an ortholog as any gene that encodes a molecule having a *functional equivalency* to the synthetic multivulval genes. It would be readily apparent to a skilled artisan in the field that since all of the possible functions of the synthetic multivulval gene products are not known, it would be impossible to know what molecules would be considered to be functional equivalents. Conversely, even if

> the exact function for the ortholog was defined, it would be impossible
>
> to know all of the molecules that might have that function.... It is unquestionable that claim(s) 1-4 is/are broad and generic, with respect to all possible compounds encompassed by the claims.

Claim 1 as amended no longer recites the term "ortholog." This basis for rejection is now moot.

Amended claim 1 and new claims 23, 27, and 31 (and their respective dependent claims) are directed to a loss of function mutation in a nucleic acid having at least 95% identity to SEQ ID NO: 24, 26, 28, and 2, respectively, and a second loss of function mutation in a Class A synthetic multivulval gene.

In finding adequate written description in the specification for sequences that are 95% identical to a given sequence and have a given activity, Example 14 of the Revised Interim Written Description Guidelines Training Materials available on the U.S.P.T.O. website under http://www.uspto.gov/web/menu/written.pdf state:

> A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

Applying the Guidelines to the present case, Applicants note that the specification identifies *lin(n3628)*, *lin(n4256)*, *lin-65*, and *mep-1* as having tumor suppressor activity (page 76, lines 7-20) and identifies the structural characteristics of the nucleic acid sequence of *lin(n3628)* (SEQ ID NO: 24), *lin(n4256)* (SEQ ID NO: 26), *lin-65* (SEQ ID NO: 28), and *mep-1* (SEQ ID NO: 2) (*see*, page 6, lines 3-9). The specification also teaches functional assays, namely genetic experiments (page 48, line 1 to page 49, line

10) and complementation assays (page 50, lines 17-29), by which one skilled in the art would be able to identify which of the nucleic acids encompassed by the claims have tumor suppressor activity. Moreover, as noted in the Written Description Guidelines, making variants of a known sequence is conventional in the art. Consistent with the above-cited Written Description Guidelines and the teachings of the specification, Applicants submit that one skilled in the art would recognize that Applicants were in possession of amended claim 1, and new claims 23, 27, and 31, at the time of filing.

As noted above, amended claim 1 and new claims 23, 27, and 31 further require a second loss of function mutation in a Class A synthetic multivuval gene. Applicants submit that one skilled in the art would understand what nucleic acids are encompassed by the term "Class A synthetic multivulval gene." At the time of filing, a number of Class A synthetic multivulval genes were known in the art. In addition, the specification: (1) teaches two Class A synthetic multivulval genes (i.e., *lin-15A* and *lin-38*; *see*, pages 29-30, Table 1 and page 54, Table 5); (2) recites a database where the structural features of the Class A synthetic multivuval genes may be obtained (page 80, lines 8-15); and (3) states synthetic multivulval genes have tumor suppressor activity (page 76, lines 7-20). In sum, Applicants submit that one skilled in the art would recognize that Applicants were in possession of the method of amended claim 1, and new claims 23, 27, and 31, at the time of filing and respectfully request that this basis for rejection be withdrawn.

Enablement

Claims 1-4 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. In particular the Office states (pages 7and 8):

> [T]he specification, while being enabling for: a method for identifying a compound that may have potential as a compound that treats a neoplasia, comprising: contacting a *C. elegans* vulval precursor cell comprising a "loss of function" mutation in a Class B synMuv gene and a second "loss of function" mutation in a "Class A synthetic multivulval gene" (or

> functional ortholog thereof), with a candidate compound, does not reasonably provide enablement for a method for identifying a compound that treats a neoplasia.

Amended claim 1 now recites "a method for identifying a *candidate* compound for treating a neoplasia." Applicants submit that amended claim 1 is directed to a method for the identification of a candidate compound that may be useful for the treatment of neoplasia. As is understood by individuals in the field of drug discovery, further testing of a candidate compound may be required to validate the ability of a candidate compound to treat a neoplasia in a mammal. This basis for rejection should be withdrawn.

As a second basis for the enablement rejection, the Office states (page 10):

> Claim 1 recites "contacting a cell" which reads on all cell types. However, the model for synMuv Class A and Class B mutants is performed using precursor vulval tissue in the nematode *C. elegans*...

Applicants submit that given (1) the Examples in the specification and (2) the high degree of structural and functional homology between members of the synthetic multivuval signaling pathway and members of the ras-signaling and Rb-signaling pathways; one skilled in the art of molecular biology would recognize that the method of amended claim 1 and new claims 23, 27, and 31, could predictably be carried out in other cells (for example, additional nematode cell types and mammalian cells).

As the Office has noted above, the specification teaches the use precursor vulval tissue to perform the method of amended claim 1 and new claims 23, 27, and 31. In addition to the teachings of the specification, Applicants submit that, at the time of filing, the high degree of structural and functional homology between the members of the synthetic multivulval signaling pathway to members of the ras-signaling and Rb-signaling pathways was recognized in the field of molecular biology (*see*, Exhibit 1, Santos and Nebreda, *FASEB J.* 3:2151-6163, 1989). Santos and Nebreda state (page 2152, left column, second paragraph):

> *Ras* genes appear to be ubiquitous in eukaryotic cells, and yeasts are the lowest organisms found to possess functional *ras* genes. The remarkable degree of conservation between species as far apart in evolution as yeast and human strongly suggests that *ras* gene products play a fundamental role in key cellular processes.

The specification further states (page 1, lines 19-28):

> Retinoblastoma (Rb) family proteins are mammalian tumor suppressors that regulate cell proliferation. This pathway is conserved among a variety of species, including the nematode, *Caenorhabditis elegans*. LIN-35 Rb, which is the nematode *C. elegans* counterpart of mammalian Rb, is required for normal vulval development in *C. elegans*. (Emphasis added).

Applicants submit that given the teaching of the specification and the high degree of structural and functional conservation between members of the synthetic multivulval signaling family and members of the ras-signaling and Rb-signaling families, one skilled in the art of molecular biology would recognize that the method of amended claim 1, and new claims 23, 27, and 31, could be performed in a number of cells, including different nematode cell types and mammalians cell types. This basis for rejection should be withdrawn.

The Office further states (page 10):

> Claim 1 also reads on *any* first mutation and any second mutation but the use of a "loss of function" mutation, or a "gain of function," or "non-functional" mutation would all result in different outcomes of this method. Claim 1 also reads broadly on a second mutation in a synMuv gene but the specification clearly teaches that the synMuv Class B gene must accompany the synMuv Class A mutation because of the functional redundancy of the synMuv class A genes.

Amended claim 1 is directed to "a *loss of function* mutation in a *Class B synMuv gene* having at least 95% sequence identity to SEQ ID NO: 24 and a second *loss of function* mutation in a *Class A synthetic multivulval gene*." New claims 23, 27, and 31, are likewise directed to a "loss of function" mutation in a Class B synMuv gene and a

second "loss of function" mutation in a Class A synthetic multivulval gene. This basis of rejection may be withdrawn.

As a further basis for rejection under 35 U.S.C. § 112, first paragraph, the Office states (page 10):

> Claim 1 also reads broadly on *any* phenotypic alteration that could occur in said cells as a result of contact with said candidate compound. However, it is not indicated how *any* alteration in a cell's phenotype (claims 1-3), which occurs as a result of contacting said cells with *any* candidate compound, in comparison to a control cell could be interpreted to indicate that the said compound is therefore a compound that treats a neoplasia.

Claim 1 has been amended to recite "cell proliferation" as the phenotype. New claims 23, 27, and 31 are also directed to detecting cell proliferation. Cell proliferation is a well-known hallmark of a neoplasia and therefore, this basis for rejection should be withdrawn.

As a last basis for the lack of enablement rejection, the Office states: "the prior art teaches that the use of isolated mammalian cells are not predictable models of cancer" (page 11). The Office further quotes from Zips et al. (*In Vivo* 19:1-7, 2005; page 3, column 2):

> It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential. (Emphasis added).

Amended claim 1 and new claims 23, 27, and 31 are directed to a method of *identifying* "a *candidate* compound for the treatment of a neoplasia." As stated above, it is well-known that further testing of a candidate compound identified in a screening assay

may be required to validate the ability of a candidate compound to treat a neoplasia in a mammal. This basis for rejection should be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1, 2, and 4 are rejected under 35 U.S.C. § 103 as unpatentable over Duyk et al. in view of Unhavaithaya et al. As the basis for the rejection, the Office states (page 14):

> Dyuk *et al.* teaches mutations in Rb or Rb-like genes, and in the lin-12 and lin-31 genes....Dyuk *et al.* teaches using Class B synMuv mutants but fails to explicitly teach one of the Class B synMuv mutant genes: Mep-1 gene, lin(n3628), lin(n4256), or lin-65. Unhavaithaya *et al.* (see abstract) teaches using a mutated MEP-1 gene for double-mutant Class B synMuv pathway experiments.

The subject matter, which is the basis of the rejection under 35 U.S.C. § 103, is now recited in new claim 31, and its dependent claims: a mutation in *mep-1* and a mutation in a second synthetic multivulval gene.

As noted above, new claim 31, and its dependent claims, are entitled to benefit of the filing date of Provisional Application Serial No. 60/410,160 filed September 12, 2002. The September 12, 2002 date is prior to the December 27, 2002 publication date of Unhavaithaya et al. Accordingly, Unhavaithaya et al. is not available as prior art against new claim 31, and its dependent claims. Applicants submit that the other cited reference, Duyk et al., alone fails to disclose a mutation in *mep-1* and therefore, does not teach or suggest every limitation of new claim 31. The rejection of claim 31 and its dependent claims under 35 U.S.C. § 103 should be withdrawn.

With regard to amended claim 1 and new claims 23 and 27, Applicants submit that Duyk et al. and Unhavaithaya et al., even if combined, fail to describe a mutation in *lin(n3628)*, *lin(n4256)*, or *lin-65*. As such, Duyk et al. in combination with Unhavaithaya et al. fails to teach or suggest each and every element of amended claim 1, and new

claims 23 and 27. Therefore, the rejection of amended claim 1, and new claims 23 and 27 (and their respective dependent claims), for obviousness under 35 U.S.C. § 103 should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including October 30, 2007, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date October 30, 2007

Kristina Bieker-Brady, Ph.D.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045